Metabolic Abnormalities of Hypertension

A Lesson in Complexity

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In this issue, Reaven and coworkers¹ report on carbohydrate and lipid abnormalities in yet another experimental model of hypertension, the Dahl rat. Whether salt-sensitive or salt-resistant, animals of this strain are hyperinsulinemic and dyslipidemic. This finding strengthens the contention that in essential hypertension, metabolic disorders such as reduced glucose tolerance, dyslipidemia, and hyperinsulinemia/insulin resistance are inherent features rather than incidental findings.

To what extent does this concept apply to human essential hypertension? The notion that in patients with high blood pressure, both carbohydrate intolerance and lipid changes are more frequent than expected on the basis of chance alone is not new and emerges consistently from shrewd clinical observation. More or less consciously, however, clinicians have written off these metabolic abnormalities as due to the obesity that so often accompanies hypertension. In the obese person, glucose tolerance tends to be worse, serum triglycerides higher, and high density lipoprotein (HDL) cholesterol lower in comparison with the lean person matched for age, gender, and body fat distribution. In addition, obesity is a classic state of hyperinsulinemia and insulin resistance. Another element is that hypertension is strongly age-related just as are a decline in glucose tolerance and an increase in the circulating levels of total cholesterol and triglycerides. Finally, treatment with some antihypertensive drugs, in particular thiazide diuretics and β-blockers, has repeatedly been shown to have adverse effects on the metabolic profile of the hypertensive patient. These facts suggest a paradigm in which aging, overweight, and drug-related effects are responsible for bringing hypertension and glucose/lipid disorders together. In this view, the relation of the latter to the former is extrinsic; they are parallel branches of diverse origin, which environmental factors force to overlap.

The young, lean, untreated hypertensive patients with definite (and otherwise unexplained) metabolic abnormalities clearly do not fit in this view. In such patients, significant insulin resistance has been shown to be present when compared with age- and weight-matched normotensive individuals.² ³ Furthermore, it has been demonstrated that this insulin resistance is both tissue-specific (predominantly located in skeletal muscle) and pathway-specific (insulin-stimulated glycogen synthesis is impaired but insulin actions on lipid, protein, and electrolyte metabolism are unaffected).⁴ ⁵ These observations intimate that the traditional paradigm is insufficient. Age may amplify the overlap of hypertension with metabolic changes, some antihypertensive drugs may have metabolic side effects, obesity (and its metabolic correlates) may act as a confounder (a potent one but still a confounder). However, underlying these reinforcing circumstances there exists an intrinsic link between essential hypertension and glucose/insulin/lipid changes, as "essential" a link as the hypertension itself.

Additional evidence bearing on this formulation is:

1) Epidemiological surveys as well as case-control analyses⁶ ⁷ show that nonobese, relatively young patients with uncomplicated hypertension have mild elevations in fasting or postglucose plasma glucose concentrations, raised serum triglycerides and total cholesterol, and reduced HDL cholesterol levels independent of antihypertensive treatment. Hyperinsulinemia, both in the fasting and the glucose-stimulated state, is there to mark the presence of insulin resistance.

To estimate the overall prevalence of these metabolic abnormalities in hypertension is, to some extent, a futile exercise. Like blood pressure, serum glucose, and lipids, insulin levels and insulin sensitivity are continuous variables. It takes panels of experts or regulatory committees to set cutoff values of an ever-elusive "normalcy," with the potential for endless debates and conflicting messages to the public.

2) In two unrelated animal models of hypertension (spontaneously hypertensive rats [SHR] and Dahl rats), Reaven has documented the presence of hyperinsulinemia, lipid changes, and reduced insulin-mediated glucose uptake by adipocytes in vitro.⁸ ⁹ In Dahl rats, the same abnormalities can be found in salt-sensitive as well as salt-resistant animals and are independent of the salt content of the diet.¹ In SHR rats, the impairment of insulin-mediated glucose uptake precedes the appearance of hypertension.¹° Similar changes in glucose and lipid metabolism, plasma insulin, and blood pressure can be experimentally produced also in Sprague-Dawley rats by
feeding them high fructose diets. These effects of fructose can be prevented by exercise training or somatostatin. These findings make for a body of cogent experimental evidence, although for the sake of fairness, one should mention that neither SHR nor Dahl rats have been found to be insulin resistant in vivo during euglycemic hyperinsulinemia.

3) In schoolchildren surveyed in Bogalusa, Louisiana, both glucose and insulin concentrations predicted higher blood pressure levels, and parental history of diabetes was associated with higher cholesterol. In the San Antonio Heart Study, hyperinsulinemia in nondiabetic offspring of diabetic parents was associated with a higher prevalence of hypertension. Perhaps more importantly, subclinical changes in glucose tolerance, lipid levels, and insulin concentrations coexist with slight elevations in both systolic and diastolic blood pressure in healthy subjects 8 years before high blood pressure develops. Indeed, among these prehypertensive individuals, those with a normal body weight have a pattern of metabolic changes that is even worse than those who are overweight. (With regard to the latter point, it is of further relevance that in a recent large prospective study, lean hypertensive patients had higher cardiovascular mortality rates than other hypertensive patients.) In the aggregate, this evidence indicates that metabolic abnormalities and hyperinsulinemia may precede the development of hypertension (and obesity), and that a genetic background of diabetes behaves like a risk factor not only for diabetes but also for hypertension.

In summary, in considering the metabolic abnormalities of hypertension, a shift from the traditional paradigm is justified by three separate arguments: independence (from obesity and other possible confounders), co-inheritability (in animal models as well as in humans), and antecedence (hyperinsulinemia/insulin resistance foreruns clinical hypertension).

These are the facts to date, of which many are associations or risk factors rather than cause/effect relations.

Reaven has hypothesized the existence of a distinct syndrome in which glucose intolerance, high blood pressure, dyslipidemia, and insulin resistance are the chief features. Note that in Reaven’s terms, syndrome X is a hierarchic cluster, that is, insulin resistance is the primary abnormality, which causes or “pulls” the others. However, available information would seem to be insufficient to establish this primacy. Reaven himself, in tandem with colleagues at the University of Parma, Italy, has shown that the simple strategy of selecting healthy persons on the basis of their higher plasma insulin concentration reproduces the infamous cluster of metabolic deviations (higher glucose, blood pressure, lipids) vis-à-vis healthy Italians with relatively less circulating insulin. Although this finding does suggest that one is dealing with intrinsically consensual variables, it does not tell which is causing which. Some suspect that essential insulin resistance materializes in the subjects in whom atherosclerosis and its sequelae develop in the absence of the classic atherogenic risk factors. (See note added in proof.) For example, a family history of premature ischemic heart disease is a strong, independent risk factor for atherosclerotic vascular disease, and it is possible that insulin resistance/hyperinsulinemia may indeed be the basis for such lineage. Although much in this area will be learned from prospective population surveys, we still lack conclusive evidence as to whether and how hyperinsulinemia or insulin resistance “makes” atherosclerosis.

For the time being, more prudent than a “syndrome,” is a scheme (Figure 1) that envisions a network of physiologically interrelated functions (body weight, glucose tolerance, insulin secretion and action, lipid metabolism, and blood pressure) among which insulin action occupies a central position because it is the most obvious common link. The nature
of the connections (physiological mechanisms) is well known for some paths in the network, imperfectly understood for others. For example, we understand how weight gain reduces insulin sensitivity, thereby straining the \( \beta \)-cells of the endocrine pancreas to oversecrete insulin; in predisposed individuals, this stress results in glucose intolerance, whereas the attendant hyperinsulinemia, coupled with augmented free fatty acid supply, invariably stimulates the liver to produce an excess of very low density lipoprotein triglycerides. On the other hand, at present the interrelations between insulin concentrations or insulin action and blood pressure are not clear, despite a number of intriguing possibilities currently under active investigation. What, if any, effect high serum lipids may have on blood pressure in vivo is still a matter of speculation.

The cloud overhanging the network in Figure 1 alludes to the genetic control of these physiological functions. The key here is that there are clear, if incompletely defined, genetic determinants for hypertension (gene HT), non–insulin-dependent diabetes (gene DB), some forms of hyperlipidemia (gene HL), and even obesity (gene OB). By extension, it is surmised that a gene for insulin resistance (gene IR) determines an individual's characteristic level of insulin sensitivity. Linkage disequilibrium is called on to explain connections between insulin resistance and disease at the genetic level.

The environment impacts on the network in the form of stress, drugs (including smoking and drinking), overeating (especially saturated fats), and sedentary habits. No one doubts the influence of these acquired factors on blood pressure, lipid profile, or glycemic control. The fact is that all these factors affect insulin sensitivity as well, and in a strikingly similar manner. For example, alcohol raises blood pressure and triglycerides, but it also reduces insulin sensitivity. Conversely, regular physical activity improves insulin sensitivity at the same time as it lowers blood glucose and lipids and keeps body size and blood pressure under check.

Ideally, if one could assign numeric values to the dual set of controls (genes and environment) and to the links in the network, then a systems engineer with experience in control theory would come up with equations describing the dynamic behavior of the network in response to perturbations: given a designated amount of hereditary drive and a stipulated quantity of environmental pressure, one could calculate the likelihood that a person will present with a specified assortment of metabolic and hemodynamic variables. In addition, it would be possible to model the feedback of any given alteration (e.g., high blood pressure or hyperinsulinemia) on gene expression. Although at present this sounds like Faust's dream, we should be prepared to deal with complexity. In our reasoning, or under controlled experimental conditions, issues and events may be kept tolerably simple. In the real world, multiple interactions, nonlinearities, and occasionally, chaotic behavior creep on stage to greatly complicate the scene. The very least we can say now is common sense: in a network, stretching any knot (for instance, blood pressure) out of the tolerance boundaries (resulting in hypertension) will drag neighboring knots along, with different solidity, eventually producing a mixture of clinical and subclinical abnormalities. Thus, the initiating cause can be diverse (including obesity) depending on the genetic makeup, and yet the consequences can be equivalent.

Postulating a network or cluster where previously there existed separate problems offers potential advantages. Clinicians may become increasingly aware that diagnosing one member of the cluster mandates screening for the others and that selecting one mode of therapy for one condition may have disturbing effects for the partners. Investigators may combine their experimental approaches. For example, direct methods for measuring insulin resistance can be used to identify subgroups at high risk for the cluster; in these subjects, specific genetic defects can then be searched. Vascular structure and reactivity can be investigated in insulin-resistant individuals to establish the relations between hemodynamics and metabolism in peripheral tissues. It is easy to foresee fertile ideas, new knowledge, and useful information. After all, networks typically are tools for exchange and integration.

**Note added in proof.** Since this Editorial Comment was written, Laakso and coworkers have directly demonstrated (by the insulin clamp technique) the presence of insulin resistance in subjects with asymptomatic atherosclerosis but normal body weight, glucose tolerance, blood pressure, and serum lipid levels.

**References**


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